REMARKS

Status of Claims

Claims 1,3,6,7, 9-12 and 14-27 are pending. Claims 1,3,6,7, and 9-12 have been rejected. Claims 1 has been amended. Support for the amended claim can be found throughout the specification, for example in paragraphs 0064, 0065, and 0067.

New claim 28 has been added. Support for the new claim can be found throughout the specification as published, for example in paragraphs 0088, 0094, and 0095. Applicants respectfully assert that no new matter has been added.

Applicants respectfully assert that the amendments to the claims add no new matter.

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1, 3 and 6, 7, 9-13 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Fontenot et al. (*The Journal of Clinical Investigation*. 112(5). 2003). ("Fontenot").

The Examiner asserts that Fontenot allegedly teaches a method wherein peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) cells from subjects diagnosed with chronic beryllium disease (CBD) are stained with monoclonal antibodies to CD4, CD8 and CD28 in order to identify the lymphocyte (T-cell) population and contacting the identified BAL T-cell subpopulation with the intracellular protein strain CFSE.

Applicants respectfully disagree. Applicants note that amended claims recite the use of a viability marker in combination with a cell proliferation marker. As per the inventor's declaration provided with this response, usage of a viability marker allows the exclusion of dead cells and further allows accurate measurement of cell proliferation. Thus the present invention provides a distinct and unexpected advantage over Fontenot in that it allows for the accurate clinical assessment of beryllium sensitivity in subjects that have been exposed to beryllium, and in normal subjects. A skilled artisan would not readily foresee in a predictable manner that combining a cell proliferation marker and a viability marker would allow for the

accurate clinical assessment of beryllium sensitivity in subjects exposed to beryllium and in normal subjects.

In addition, as per the inventor's declaration, Fontenot's describes how the function of the BAL cells was impaired by decreased CD28. Indeed Fontenot states that:

> Here, we examined the role of CD28-mediated costimulation in antigen-specific T cell activation and survival. The results demonstrate an apparent evolution of independence from CD28-mediated costimulation that correlates with memory cell differentiation. Memory $CD4^+$ T cells in blood continued to require CD28 costimulation for proliferative and cytokine responses to beryllium. In the lung, proliferation and secretion of Th1-type cytokines by effector memory cells were functionally independent of CD28 costimulation, and a proportion of these cells stopped expressing CD28. These $CD4^+CD28^-$ T cells showed decreased proliferative capacity and an increased rate of apoptosis after stimulation with antigen, suggesting transition to a presenescent state.

(See, Fontenot p. 777, top-left paragraph). Hence, Fontenot's does not describe nor suggest a predictive response of PBMC to beryllium salt (as measured by CFSE) as a disease indicator, as the present invention demonstrates (see paragraphs 0096-0099).

In summary, Fontenot does NOT use CFSE and a viability marker to measure the proliferation of $CD3^+/CD4^+$ peripheral T cells and thus does not address the differences in this response between normal subjects and subjects exposed to beryllium. Therefore, Fontenot does not render the present invention obvious.

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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